# Essential thrombocytosis: Underemphasized cause of large-vessel thrombosis

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***Purpose:*** **The purpose of this study was to describe the clinical course of patients seen with large-vessel thrombosis in association with essential thrombocytosis (ET).**
***Methods:*** **This study was a retrospective review of all patients treated for large-vessel thrombosis caused by ET during a 2-year period at University of Washington teaching hospitals.**
***Results:*** **Five patients presented with arterial (femoral-popliteal-tibial: aortic), portal (two cases), or systemic venous (inferior vena cava) thrombosis and required operation. Two were known to have ET; in three others ET was diagnosed after operation when platelet counts persistently in excess of 500,000/mm$^3$ were noted. The diagnosis of ET was established in each case by ruling out causes of reactive thrombocytosis and (in the three new cases) by evidence for megakaryocyte hyperplasia on bone marrow biopsy. Platelet counts in all five patients were reduced to normal levels by cytoreductive therapy, and no further thrombotic episodes have occurred during 18 months (mean) of follow-up. During this 2-year period ET accounted for more large-vessel thrombotic complications in our institutions than all other more frequently described hypercoagulable states combined.**
***Conclusions:*** **ET is an underemphasized cause of large-vessel thrombosis. (J VASC SURG 1995;22:443-9.)**

The hypercoagulable state is characterized by multiple or concurrent episodes of arterial or venous thrombosis, vascular occlusion at an early age or in unusual sites, or thrombosis in multiple family members. Much recent attention has been given to various thrombophilic states that may either be inherited (deficiencies of protein C,[1] protein S,[2] and antithrombin III,[3] or abnormal plasminogen[4]) or acquired (heparin-associated thrombosis,[5] antiphospholipid antibodies,[6] or activated protein C resistance[7]). Although thrombosis in association with an abnormally elevated platelet count is well recognized by hematologists,[8-10] this phenomenon has rarely been mentioned in the vascular surgical literature.

The myeloproliferative disorders (MPDs) are a heterogeneous array of conditions that include polycythemia vera, chronic myelogenous leukemia, myeloid metaplasia with myelofibrosis, and essential thrombocytosis. All may variably be associated with hemorrhagic or thrombotic complications, the incidence of which may vary with the specific condition. Essential thrombocytosis (ET) is defined by the absence of other MPDs or conditions that result in a reactive rise in platelet count and demonstration of autonomous platelet production. Patients with ET have been reported to manifest symptoms and signs either of *bleeding,* usually as ecchymoses or mucosal hemorrhage, or of *thrombosis,* with the usual presentation being cutaneous or digital ischemia. Thrombosis of large arteries or veins requiring operative intervention has only occasionally been reported in patients with ET.[11,12]

Five patients treated with operation at University of Washington teaching hospitals for arterial or venous thrombosis were found to have ET. The clinical course of these patients illustrates the need for prompt recognition and appropriate treatment of this condition.

## CASE REPORTS

In a 2-year period eight patients fulfilling diagnostic criteria for ET and manifesting symptoms and signs of major arterial or venous thrombosis were evaluated. Five underwent an operative intervention and are discussed in detail.

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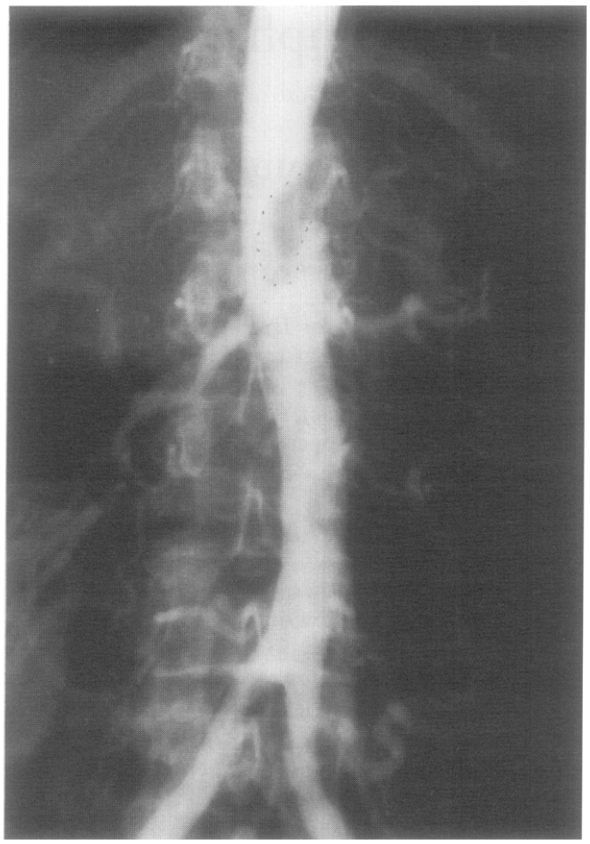

**Fig. 1.** Contrast aortogram in elderly woman with known ET and complaints of abdominal pain, intestinal angina, and kidney failure reveals large aortic mural thrombus occluding origins of celiac axis and superior mesenteric artery (case 2). At operation large platelet thrombus was found adhering to supraceliac aorta.

**Case 1.** A 44-year-old white woman with a history of hypertension, obesity, and tobacco use presented with an ischemic right leg. She reported minor trauma to her right foot 13 days before admission with progressive symptoms of parasthesia, rest pain, and cutaneous infarction. The patient was admitted to an outside hospital, and when an arteriogram demonstrated diffuse femoral, popliteal, and tibial artery occlusion, thrombolytic therapy was attempted. This procedure was unsuccessful, and the patient was transferred.

Hematologic workup demonstrated a platelet count of 780,000/mm$^3$. Further blood test results including prothrombin time, partial thromboplastin time, fibrinogen, antithrombin III, protein C, protein S, and white blood cells were within normal limits. Bone marrow biopsy demonstrated megakaryocyte hyperplasia. The patient underwent a right groin exploration with attempted thrombectomy; this procedure was unavailing, and a right through-knee amputation was ultimately required. Arteriographic and histopathologic evaluation of her arteries demonstrated no evidence for atherosclerosis or other arterial wall disease. Treatment after surgery included aspirin and hydroxyurea. Three-year follow-up demonstrated no further episodes of thrombosis; her most recent platelet count was 277,000/mm$^3$.

**Case 2.** A 68-year-old white woman with known ET presented with abdominal pain, intestinal angina, and mild kidney failure. She was found on aortography (Fig. 1) to have thrombus in the aorta with occlusion of the celiac and superior mesenteric arteries and splenic, renal, and hepatic infarcts consistent with embolic phenomena. Hematologic workup at the time of admission was significant for a platelet count of 1,000,000/mm$^3$. The patient underwent transaortic celiac and superior mesenteric artery exploration; large platelet thrombi were removed from the aorta itself and from the orifices of the visceral arteries. No evidence for aortic or mesenteric arteriosclerosis was noted at the time of operation. Postoperative treatment with hydroxyurea resulted in normalization of platelet count, her most recent value being 87,000/mm$^3$. She has manifested no further thrombotic events at 2½ years of follow-up.

**Case 3.** A 46-year-old male triathlete with known ET was admitted with upper gastrointestinal hemorrhage. Upper endoscopy revealed grade 4 esophageal varices. Liver function studies were normal. Further imaging studies revealed thrombosis of the portal, superior mesenteric, and splenic veins and massive splenomegaly. Hematologic workup showed normal protein C and S and antithrombin III levels: the platelet count was 580,000/cu mm despite chronic treatment with hydroxyurea. Because of the necessity to control recurrent variceal hemorrhage, a modified Sugiura procedure was performed, including splenectomy, esophagogastric devascularization, and distal esophageal staple transection.[13] After operation the patient was maintained on aspirin and an increased hydroxyurea dosage, with his most recent platelet count at 126,000/mm$^3$. He was symptom free at 6-month follow-up.

**Case 4.** A 33-year-old woman was admitted to another hospital with abdominal pain and jaundice. Liver functions were diffusely abnormal: liver biopsy showed centrilobular hepatocellular necrosis without cirrhosis. She was transferred when she had massive upper gastrointestinal hemorrhage seen on upper endoscopy to be arising from large esophageal and gastric varices. Splanchnic angiography revealed diffuse venous thrombosis with no "shuntable" vessel opacified. She had peritonitis and underwent emergency exploratory celiotomy, at which time extensive small-bowel infarction was discovered. Resection of all but 120 cm of viable small bowel was undertaken: transection of mesenteric veins showed grey platelet-fibrin thrombi. Because of the presumption that the patient had had a venous intestinal infarction, operative steps were taken to reduce her portal hypertension by means of a modified Sugiura procedure (see Case 3).

The patient had a complicated postoperative course because of "short-gut" syndrome, an anastomotic leak resulting in an enterocutaneous fistula, and thrombosis of both her right subclavian vein and her left iliofemoral venous system. Her platelet count was discovered to be

780,000/mm³. Although this finding was thought initially to be a secondary postsplenectomy thrombocytosis, elevated preoperative platelet counts varying from 580,000 to 840,000/cu mm were belatedly discovered; a platelet count drawn during an uncomplicated pregnancy 2 years previously had been 720,000/mm³. Bone marrow biopsy demonstrated megakaryocyte hyperplasia. ET was diagnosed, and when postoperative platelet counts rose to 1,200,000/mm³, hydroxyurea was started. Six months after operation she is maintaining her weight without parenteral nutrition and has a platelet count of 360,000/mm³.

**Case 5.** A 68-year-old woman with abdominal pain presented with what was diagnosed as a primary or secondary tumor of the inferior vena cava and left renal vein ostium (Fig. 2). Operative exploration showed a caval mass that on histologic examination proved to be organized thrombus. It was then noted that her platelet count was 734,000/mm³. All other studies supporting the diagnosis of a hypercoagulable state were negative, and bone marrow biopsy showed megakaryocyte hyperplasia. Aspirin and hydroxyurea reduced the platelet count to 220,000/mm³, and she has manifested no further thrombotic episodes at 2½-year follow-up.

During the 2-year period under review, three patients with other thrombophilic states (two with antithrombin III deficiency[3] and one with anticardiolipin antibody[6]) had a large-vessel thrombosis and required operation in the University of Washington hospitals system.

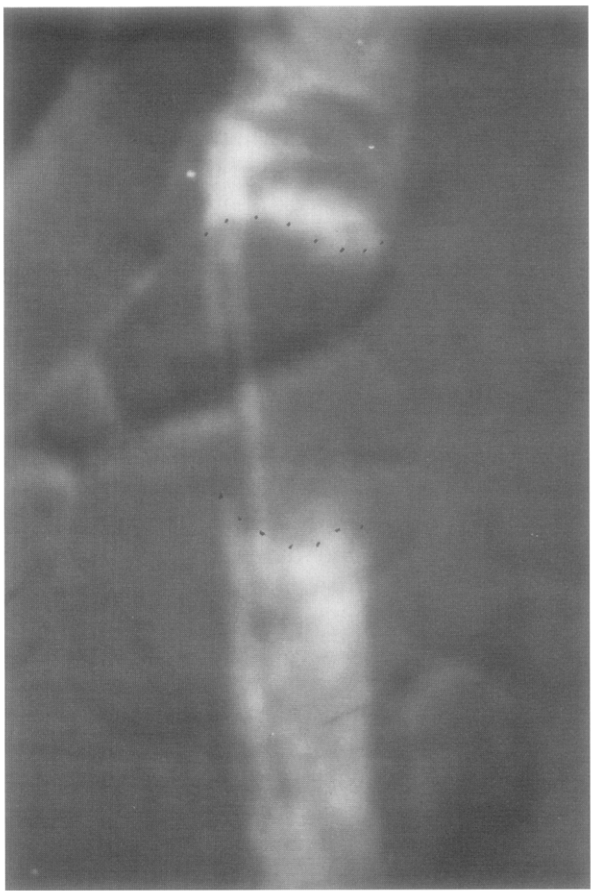

**Fig. 2.** Inferior vena cavography in elderly woman with diffuse abdominal pain and intracaval mass on abdominal computed tomographic scanning shows bulky lesion considered to be primary or secondary venous wall neoplasm before operation. At abdominal exploration lesion was found to be organized thrombus, and discovery of chronically elevated platelet count led belatedly to diagnosis of ET.

## DISCUSSION

A recent interest in various inherited and acquired hypercoagulable states has manifested itself in the vascular surgical literature[14-17]—appropriately so, because patients afflicted with such disorders are increasingly likely to be seen by vascular surgeons, and reconstructive procedures undertaken in such patients are threatened by their underlying prothrombotic state.[16] Thrombophilias caused by deficiencies of various coagulation proteins[1-3] or the presence of abnormal antibodies or enzymes[4-7] has been emphasized. Accordingly, we were surprised to discover that, in our institution, the most common cause of a hypercoagulable state resulting in symptomatic large-vessel occlusion during a recent 2-year period arose from essential or primary thrombocytosis.

ET has been defined by the Polycythemia Vera Study Group[18] as a persistent thrombocytosis greater than 600,000 platelets/mm³, confirmed by a bone marrow biopsy demonstrating megakaryocytic hyperplasia. However, hematologists do not strictly adhere to this platelet count requirement; a platelet count of 500,000/mm³ or greater is considered adequate for diagnosis. Furthermore the diagnosis of ET may be established simply by ruling out known causes of reactive thrombocytosis. ET is a diagnosis of exclusion; more common secondary causes of an elevated platelet count (e.g., splenectomy, other myeloproliferative disorders, occult malignancy) must be ruled out. Reactive thrombocytosis can also result from iron deficiency anemia, acute blood loss, inflammatory bowel disease, or various rheumatologic disorders. Although the terms "thrombocythemia" and "thrombocytosis" have been used interchangeably for this condition, thrombocythemia is defined as an abnormal proliferation of megakaryocytes on bone marrow biopsy; thrombocytosis is defined as an increase in the number of platelets in the blood and is ET only when this elevation in platelet count is a primary process.

ET was first described in 1934[19] and until recently was considered a relatively rare disorder. Presumably as a result of an increase in platelet counts obtained at the time of other blood tests, the condition is being detected more often in asymptomatic patients. By definition the platelet count is elevated; however, the risk of a bleeding or thrombotic complication does not necessarily correlate with the platelet count.[11] The discordance between platelet count and thrombotic risk has raised the question of platelet function in ET. Numerous studies addressing this issue have been performed; no consistent abnormalities have been found, and patients with ET generally exhibit normal bleeding times. Results of platelet aggregometry have been variable: Tobelem et al.[20] report that platelet aggregation is elevated "in almost all cases," whereas Kaywin et al.[21] found diminished platelet aggregation in response to epinephrine and other conventional platelet aggregating agents.

Complications of ET vary from small to large vessels, from arterial to venous sides of the circulation, and from hemorrhagic to thrombotic presentations. When *hemorrhagic* complications occur, they usually involve mucosal or gastrointestinal hemorrhage, epistaxis, or postoperative bleeding. The most frequent *thrombotic* complication is one of various disturbances of the microcirculation—livedo reticularis,[22] erythromelalgia,[23] migraine,[24] or cerebrovascular ischemia.[25] In a series reported by Hehlmann et al.,[26] thrombotic involvement of the microcirculation was the presenting factor in 67% of cases. Symptoms included digital cyanosis, pain, parasthesias, ulceration, and frank gangrene. Thrombotic complications of large vessels have also been reported in from 18% to 51% of patients in various series.[12,27,28] An obvious explanation for the differences among these studies is the rate of incidental discovery of asymptomatic patients with ET.

Like platelet function studies, adjunctive risk factors for thrombotic and hemorrhagic complications vary among reported series of patients with ET. Hehlmann et al.[26] correlated an increased risk for thrombotic events in patients with ET with concurrent smoking, hypertension, or diabetes.[26] McIntyre et al.[24] studied complications associated with ET in a series of 56 patients younger than 40 years: "life-threatening" complications were observed in 5% of patients and "significant" complications in 33%.[24] Nonetheless they concluded that because the risk of major complications in young patients is low, intervention should be reserved for those patients with significant thrombotic or hemorrhagic symptoms, because first-line medications carry their own set of risks. Patients with ET have 5- and 10-year survival rates only minimally less than age-matched patients in a control group[10,24,29]: a small percentage of such patients undergo transformation to another MPD or to acute leukemia.[30]

Thrombotic events associated with ET suggest platelet hyperaggregation, although (as noted previously) whether platelets in ET function abnormally remains in dispute. Thus the first line of therapy is the administration of platelet antiaggregating agents such as aspirin; ticlopidine might be expected to be effective as well, although it has not been tested in this setting. Patients with microcirculatory symptoms—migraine, erythromelalgia, livedo reticularis—tend to respond particularly well to this therapy. Anticoagulants have generally been ineffective in the management of the thrombotic complications of ET—perhaps not surprisingly in view of the apparently dominant role played by platelets in this condition. Anagrelide, an agent that retards platelet aggregation by inhibiting cyclic nucleotide phosphodiesterase and release of arachidonic acid and also lowers platelet count by an unknown mechanism, is being evaluated for its safety and efficacy in patients with ET.[31]

Acute reduction of platelet count is most readily effected by platelet pheresis[32] and is prudent when bleeding or thrombotic complications occur in patients with ET whose platelet count exceeds 1 million. Prevention of recurrent thrombosis is best accomplished with aspirin or intravenous dextran. Prophylaxis is generally unwarranted in the authors' view, unless a markedly elevated platelet count occurs in a patient with other thrombotic risk factors, for example, symptomatic atherosclerosis. Long-term medical management, considered indicated once a major hemorrhagic or thrombotic complication occurs, is based on the combination of antiaggregating agents, usually aspirin, and cytoreductive therapy such as radioactive phosphorus, alkylating agents, hydroxyurea, or interferon. Alkylating agents such as busulfan and chlorambucil are effective in the control of ET; however, because of these agents' leukemogenic potential, they are not recommended in younger patients,[33] whose condition at any rate generally pursues a more indolent course.[10,24,29] Like other antimetabolites, hydroxyurea inhibits DNA synthesis and thereby sharply reduces megakaryocyte population and platelet count. This agent appears to be the treatment of choice in younger patients, because animal trials have demonstrated no associated mutagenesis with hydroxyurea administration.[34]

The constitutional effects associated with interferon treatment limit its efficacy.

Although ET is a relatively benign condition, most of whose complications can be managed medically by aspirin and cytoreductive therapy, occasionally patients with ET will present with major arterial or venous thromboses and require operative intervention. Alternatively, the surgeon may be confronted by a patient presenting de novo with large-vessel thrombosis in spite of the absence of obvious atherosclerotic or other thrombotic risk factors. In such a setting a thorough evaluation to characterize possible inherited or acquired hypercoagulable states is prudent. Our experience suggests that assessing the platelet count is warranted: during a 2-year period of time in our institution ET was the leading cause of a large-vessel thrombosis requiring operative intervention, accounting for more such cases than all other more commonly emphasized thrombophilic states *combined.* We consider ET an underemphasized cause of arterial and venous thrombosis.

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## DISCUSSION

**Dr. Lloyd M. Taylor, Jr.** (Portland, Ore.). Dr. Johnson and her colleagues have brought to our attention five cases in which major large-vessel thromboses requiring vascular surgical intervention occurred in patients with essential thrombocytosis. During the 2-year period these cases were accumulated, essential thrombocytosis was the most frequently recognized hypercoagulable state in their hospital. Based on this experience, the authors recommend that we screen patients with unexplained thromboses for essential thrombocytosis and that we treat it appropriately when discovered.

Of course, unlike the situation with other so-called hypercoagulable states, screening for essential thrombocytosis is performed as a matter of routine on most hospitalized patients because of the inclusion of platelet counts in automated complete blood counts. This means that without doubt, this condition was in part the most frequently discovered hypercoagulable state in their patients because it was the one most frequently looked for.

Recognized hypercoagulable states include essential thrombocytosis, deficiencies of proteins C and S and antithrombin III, abnormalities of plasminogen and fibrinogen, heparin-associated thrombosis, the presence of antiphospholipid antibodies, and hereditary resistance to activated protein C. Conventional practice recommends evaluation for these conditions when patients have multiple or concurrent episodes of arterial or venous thrombosis, vascular occlusion at an early age or in unusual sites, or familial thromboses. Others have recommended evaluation in patients with arterial occlusions in the absence of atherosclerotic risk factors. Adherence to this practice means that these states will, of course, only be discovered in such patients. The danger of this approach to case finding is that an inappropriately morbid prognosis will be assigned to the conditions and that they will be inappropriately considered to be rare.

On our vascular surgery service, all patients undergoing operations have been screened for the presence of so-called hypercoagulable states since 1990. The tests have included proteins C and S and antithrombin III, antiphospholipid antibodies, platelet count, and, since 1994, hereditary resistance to activated protein C. What we have discovered and reported is that while deficiencies of proteins C and S and antithrombin III are indeed rare, the presence of antiphospholipid antibodies occurs frequently in patients undergoing vascular surgical procedures, approximately one third being affected. The prevalence of hypercoagulable states appears just as high in older patients with atherosclerotic risk factors as in those who are younger and lack atherosclerotic risk factors. What we have also discovered but not yet reported is that thrombotic complications including graft occlusion appear no more frequently in patients with so-called hypercoagulable states than in others with arterial disease requiring surgery. So by screening all patients and understanding the denominator, our understanding of these conditions is that they are not, as once believed, rare, and they may not, as once believed, be associated with a particularly poor prognosis.

All of this brings me to my questions for the authors. Since presumably your hospital laboratory computer has recorded platelet counts on essentially all patients in your 2-year study period, how many patients had platelet counts over 1 million but did not have thrombotic complications?

Is essential thrombocytosis with thrombotic complications distinguishable from essential thrombocytosis as a laboratory curiosity? Are there circulating platelet aggregates in symptomatic patients, as some have suggested? Finally, what is your recommendation for treatment of patients discovered to have essential thrombocytosis in the absence of symptoms? Is this truly a hypercoagulable state, deserving of prophylactic treatment, or is essential thrombocytosis a disorder that in an unknown number of those affected is associated with thrombosis?

**Dr. Marion Johnson.** Dr. Taylor, your group has provided much about what we know about the denominator of hypercoagulable states in the vascular patient population.

Regarding the total number of high platelet counts seen in this period, we do not have that information from the University of Washington hospitals. However, Buss and colleagues recently reported their 5-year experience at Bowman Gray in the *American Journal of Medicine.* Among 280 patients diagnosed with abnormally high platelet counts, 88% had reactive or secondary platelet elevations such as that which follows from splenectomy or malignancy; 12% had a primary myeloproliferative disorder. Significantly, the patients with a reactive or secondary thrombocytosis had only a 4% risk of thrombotic complications compared with the patients with a myeloproliferative disorder who had a 54% risk of thrombotic complications.

Therefore, in answer to your other questions, essential thrombocytosis does indeed appear to confer a significant likelihood of thrombotic complications, and at the least such patients' platelet counts should be followed serially. Once a complication has occurred, patients are at increased risk for repeat thrombotic complications, and their therapy should include aspirin or a cytoreductive agent. Surveillance for leukemogenic transformation should be undertaken.

**Dr. Wesley S. Moore** (Los Angeles, Calif.). I wonder if you can help me in differentiating this condition from polycythemia rubra vera. It is well known that the risk of both thrombotic and hemorrhagic complication is fairly significant in polycythemia. My understanding is that one difference is that in the case of polycythemia we have both elevation of the red cell and white cell elements. But indeed in your patients if you had an increased megacaryocyte concentration in the bone marrow, might this not be considered a variant of polycythemia and, therefore, the thrombotic complications be quite well explained?

**Dr. Johnson.** You are right. They are all myeloproliferative disorders, and as I pointed out, there is a 15% conversion to other myeloproliferative disorders. So essential thrombocytosis exists on the continuum of myeloproliferative disorders but is distinct from polycythemia rubra vera because it involves strictly the megakaryocytic component of the bone marrow and not the other blood cell precursors. I think thrombotic complications arise both from the excessive platelet production and, perhaps, from abnormalities of the ET platelets themselves.

**Dr. Peter F. Lawrence** (Salt Lake City, Utah). Dr. Johnson, in your series virtually all patients had an occlusion of either a large artery or large vein, and we have had a somewhat different experience at our institution. Most of our patients have presented with a lower extremity digital artery occlusion and ulceration of the lower extremities or a toe ulcer that has been quite painful. I am wondering whether your series is typical of what is reported in the literature and whether large-vessel thromboses are more atypical than the more common digital artery occlusion.

Second, when our patients have been treated with hydroxyurea, they have had remarkable improvement in their symptoms and often have not required revascularization and have also not required amputation. I am curious as to whether the treatment with hydroxyurea or one of the more aggressive agents to deal with this problem results in recanalization of vessels or why patients have a complete resolution of their symptoms and healing of their ulcer without what would be any apparent improvement in blood flow.

**Dr. Johnson.** Certainly microvascular thromboses associated with essential thrombocytosis are far more frequent, and perhaps the ulcers and digital ischemia involved more sludging in the microvasculature than a large-vessel thrombosis, thereby accounting for that finding. Our study did not identify patients with microvascular thromboses, just strictly those with large-vessel thrombosis requiring operation. Recanalization could indeed account for improvement in symptoms of patients with such microvascular thrombosis.

**Dr. Wiley F. Barker** (Los Angeles, Calif.). Dr. Lawrence's query stimulated me to offer the following instructive capsule history of a patient Dr. Quiñones and I shared. A woman in her seventies with a known history of thrombocytosis under treatment with hydroxyurea suddenly had pain and discoloration of both feet. Distal pulses were present, although diminished. Careful study by arteriography and magnetic resonance imaging identified a vague intraluminal filling defect in the infrarenal aorta. Operation disclosed a mass composed of platelet thrombus. It was adherent at only one small point on the posterior wall and was easily lifted free. The point of attachment showed no lesion, and the remainder of the exposed aortic wall appeared entirely innocent. She recovered but died a few years later after a stroke. I suggest that peripheral lesions in the presence of thrombocytosis should be considered as possibly being thromboembolic from a major proximal vessel.

**Dr. Johnson.** Certainly. That is a well-taken point, and reflects to a degree the scenario presented by our second patient.